Study uses genetic data to support use of thiazide diuretics for kidney stone prevention

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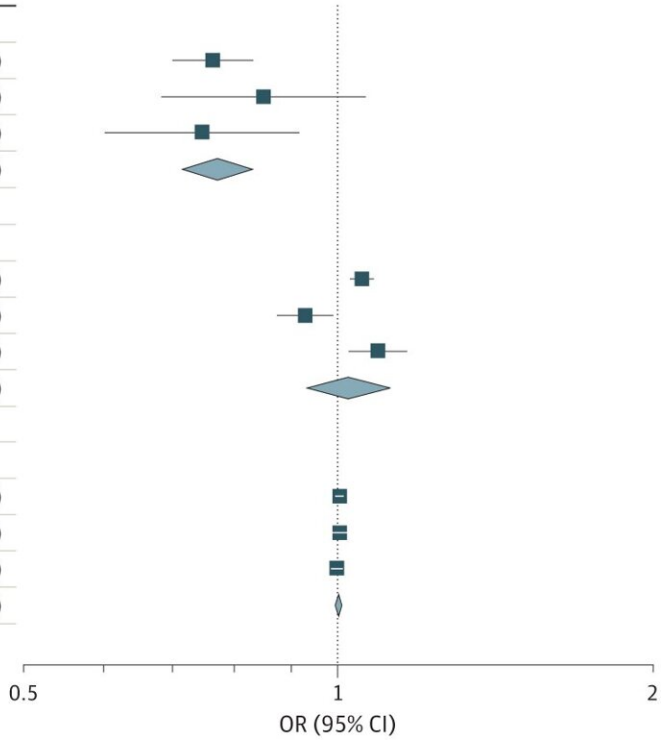
Exposure	OR (95% CI)
Thiazide diuretics	
MVP[31]	0.84 (0.80-0.89)
UKB[56]	0.90 (0.79-1.04)
FinnGen[57]	0.83 (0.73-0.95)
Total	0.85 (0.81-0.89)
Heterogeneity: $\chi^2_2 = 0.92$ ($P = .63$); $I^2 = 0\%$	
β Blockers	
MVP[31]	1.03 (1.02-1.05)
UKB[56]	0.96 (0.92-0.99)
FinnGen[57]	1.06 (1.01-1.10)
Total	1.02 (0.96-1.07)
Heterogeneity: $\chi^2_2 = 15.53$ ($P < .001$); $I^2 = 87\%$	
Systolic blood pressure	
MVP[31]	1.00 (1.00-1.01)
UKB[56]	1.00 (0.99-1.01)
FinnGen[57]	1.00 (0.99-1.01)
Total	1.00 (1.00-1.01)
Heterogeneity: $\chi^2_2 = 0.59$ ($P = .74$); $I^2 = 0\%$	



Association of Genetic Proxies of Thiazide Diuretics, β-Blockers, and Systolic Blood Pressure With Risk of Kidney Stones. FinnGenn indicates the FinnGen study; MVP, Million Veteran Program; OR, odds ratio; UKB, UK Biobank.

Kidney stones affect nearly 10% of the global population. For more than three decades, thiazide diuretics, a common medication used for high

blood pressure, have been the standard of care for kidney stone prevention because they reduce the excretion of urinary calcium.

However, recent clinical trials have raised doubts about their efficacy in preventing kidney stones. The NOSTONE trial, published in *The New England Journal of Medicine* in March 2023, failed to find a protective effect of thiazide diuretics on kidney stone disease.

A new Vanderbilt University Medical Center genetic association study of more than 1 million adults challenges those findings. The study, published in JAMA Network Open, used genetic markers to mimic the effect of thiazide diuretics to estimate the long-term medication effect.

"We found that these genetic proxies of thiazide diuretics were associated with a 15% lower risk of kidney stones," said Jefferson Triozzi, MD, the lead author and nephrology fellow pursuing a Master of Science in Clinical Investigation.

"Furthermore, we examined serum laboratory values relevant to the treatment of kidney stones and found that the genetic proxies of thiazide diuretics were associated with higher serum calcium levels, supporting the notion that thiazides affect kidney stone risk by modulating calcium excretion in the urine."

Most of the adults in the study were participants in the VA Million Veteran Program (MVP), a national research program that examines the effect of genetics, lifestyle, and other factors on veterans' health and wellness.

"The VA Million Veteran Program is the largest and most diverse biobank in the world, now with 1 million participants as of Nov. 11," said Adriana Hung, MD, MPH, associate professor of Medicine, Division of Nephrology, and senior investigator for this manuscript.

"Unique resources like the MVP, with extensive data on clinical condition combined with genomic data, provide a valuable resource for genetically informed drug discovery and drug repurposing. Thiazide diuretics are recommended by international guidelines for the prevention of calcium kidney stones with long-term safety data."

The all-VUMC team of researchers plans to investigate the underlying mechanisms by which thiazide diuretics lower the risk of kidney stones next.

"Our study highlights the importance of considering genetic proxies to estimate the long-term effects of medications and offers new evidence to support the use of thiazide diuretics for kidney stone prevention," Triozzi said. "We believe genetic data can help us understand drug mechanisms and perhaps lead to new drug discovery for kidney stone disease."

More information: Jefferson L. Triozzi et al, Mendelian Randomization Analysis of Genetic Proxies of Thiazide Diuretics and the Reduction of Kidney Stone Risk, *JAMA Network Open* (2023). DOI: 10.1001/jamanetworkopen.2023.43290

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